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poster presentations

5P MICROTUBULE-DEPOLYMERIZING AGENTS USED IN ANTIBODY-DRUG-CONJUGATES INDUCE ANTITUMOR ACTIVITY BY STIMULATION OF DENDRITIC CELLS

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Antibody drug conjugates (ADCs) are emerging as powerful treatment strategies with outstanding target specificity and high therapeutic activity in cancer patients. While >30 ADCs are currently being investigated in clinical trials, brentuximabvedotin and T-DM1 represent clinically approved ADCs in cancer patients. We hypothesized that their sustained clinical responses could be related to the stimulation of an antitumor immune response. Indeed, the two microtubule-destabilizing agents Dolastatin 10 and Ansamitocin P3, from which the cytotoxic components of brentuximabvedotin and T-DM1 are derived, may serve as prototypes for a class of agents that induce tumor cell death and convert tumor resident, tolerogenic dendritic cells (DCs) into efficient antigen presenting cells (APCs). The two drugs induced phenotypic and functional maturation of murine splenic as well as human monocyte-derived DCs. In contrast, microtubule-stabilizing agents such as taxanes did not display this feature. In tumor models, both Dolastatin 10 and Ansamitocin P3 efficiently promoted antigen uptake and migration of tumor-resident DCs to tumor-draining lymph nodes, thereby potentiating tumor-specific T cell responses. Underlining the requirement of an intact host immune system for the full therapeutic benefit of these two compounds, their antitumor effect was far less pronounced in mice lacking adaptive immunity or dendritic cells. Combinations with immune checkpoint inhibition (anti-CTLA-4/-PD-1) did further augment antitumor immunity and tumor rejection, which was reflected by reduced Treg numbers and elevated effector function of tumor resident T cells. Ultimately, we were able to demonstrate peripheral immune cell activation and brisk T cell infiltration into tumors in patients previously treated with BrentuximabVedotin. Experiments are currently ongoing to investigate the immunological mode of action of T-DM1 using orthotopic breast cancer models and patients undergoing treatment. Our data reveal a novel mode of action for microtubule-depolymerizing agents and provide a strong rationale for clinical treatment regimens combining these with immune-based therapies.

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